The Diagnosis and Treatment of Meningitis

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SUMMARY

Treatment of meningitis is no longer a question of the administration of antimeningococcal serum and awaiting results. Today there is at hand an ever expanding armamentarium of drugs effective on various bacteria, rickettsia and some of the larger viruses. The skillful use of these singly or in combination offers an excellent prognosis in most forms of bacterial meningitis. Tuberculous meningitis continues to present a poor outlook, but this has been improved with more intensive therapy. More effective agents are needed in the treatment of this disease.

"Shotgun" therapy may be indicated in critically ill patients prior to accurate bacteriological diagnosis; it is more important that therapy should include an effective agent or combination of agents than to attempt to determine in advance the most potent form of specific therapy. Partially treated purulent meningitis may be confused with aseptic meningitis. There is at present no effective therapeutic agent for the viral meningitides, but the prognosis is favorable in most of these diseases without specific therapy.

DIAGNOSIS is so intimately a part of the treatment of meningitis that the two must be considered together. A review of the disease entities which raise the suspicion of central nervous system disease will aid in consideration of specific treatment.

First in order are diseases which give rise to stiffness of the neck but in which there is no evidence of meningeal reaction or of cellular response or pleocytosis of the cerebrospinal fluid. Patients with such symptoms are frequently referred to a communicable disease unit with a diagnosis of meningitis or poliomyelitis. If pleocytosis is absent, then it is probable that the neck stiffness is caused by either extraneural disease of the head and neck or systemic disease such as bacteremia, pneumonia, pyelitis, or exanthemata. Among the extraneural causes of the symptom are trauma, tumors in the cervical region, and infections of the upper respiratory tract including the associated structures (pharyngitis, sinusitis, otitis media and cervical adenitis). Poliomyelitis will sometimes cause typical symptoms and course without provoking pleocytosis. When the stiffness of the neck is of extraneural origin, pain may interfere with any movement of the head and neck, whereas the patient with meningeal irritation usually retains all movement but flexion. Frequently, a patient with "wry neck" can flex his neck even though he cannot extend or rotate it. The signs of meningeal irritation caused by systemic infections probably are a result of actual irritation of the meningeal vessels. Bacteremia, viremia, or toxemia may provoke nuchal rigidity because of injury to meningeal vessels without pleocytosis or other evidence of actual meningeal infection. The term "meningismus" should be applied only to those cases in which actual invasion of the meninges by a pathogenic organism can be excluded. Disease of the upper respiratory tract may give rise to toxemia and meningismus in addition to local inflammatory reaction.

If the cerebrospinal fluid contains over five leukocytes or any polymorphonuclear leukocytes per cu. mm. (that is, cerebrospinal fluid pleocytosis), then meningitis in the sense of inflammatory response exists, although there is still a possibility that no infectious agent has gained entry. Tumors of the brain and brain stem, heavy metal intoxications, and so-called "neighborhood reactions" must be considered. Neighborhood reactions may arise from conditions such as abscess of the brain or of the lateral sinus. Extension of these processes into the cerebrospinal fluid by rupture of the intervening wall may convert them to frank purulent meningitides.

Hemorrhage may be confused with meningitis. In the presence of neck stiffness and coma, lumbar puncture may be necessary for purposes of differentiation. Although gross blood in the spinal fluid usually confirms the diagnosis of subarachnoid hemorrhage, in some cases there is blood in the spinal fluid of a patient with meningitis. Differentiation is made by counting both the leukocytes and the erythrocytes per cu. mm. of spinal fluid. In cerebral hemorrhage, the leukocytes are present in the same ratio to the erythrocytes as exists in the peripheral blood; in meningitis the number of leukocytes far exceeds the number accounted for in this manner.

If spinal fluid pleocytosis exists and no obvious non-infectious cause can be determined, then it must be assumed that an infectious agent is responsible. There are two main subgroups—infections by bacteria or other larger organisms and infections attributable to viruses or to virus-like agents. These are usually referred to, respectively, as purulent and aseptic meningitides. (More correctly, there should

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be included another classification, serous meningitis, in which there is less pleocytosis than in purulent meningitis; but this term is used for a specific form of tuberculous meningitis which will be referred to later.)

Meningococcal meningitis. Typically, in meningococcal meningitis, pronounced limitation of neck flexion develops in the course of a febrile illness of variable severity. Prostration may be mild or severe. Headache, fever, nausea, vomiting, restlessness, irritability, convulsions, coma, signs of cerebral irritation and increased intracranial pressure may vary widely. Especially in infancy, the evidence of central nervous system disease may be most meager. The presence of a hemorrhagic cutaneous eruption associated with meningeal irritative signs often proclaims the diagnosis. Associated rashes may be nondescript, morbilliform or urticarial and *not* of equal diagnostic significance.

The blood has a high polymorphonuclear cell content with a preponderance of immature forms and absence of eosinophils. Fluid removed at lumbar puncture is often milky white with over a thousand leukocytes—primarily polymorphonuclear—per cu. mm. Chemically, the fluid is abnormally high in protein content and low in sugar.

Bacteriological confirmation of the diagnosis rests on the demonstration of intracellular, Gram-negative diplococci in a smear of the spun sediment and/or in suitable culture media. Often the organisms are not observed on the direct smear—in fact, of all forms of bacteria causing meningitis, the meningococcus is most frequently *not* detected by direct smears or even by cultures, particularly if even minimal specific therapy has been given. However, this interference with the demonstration of organisms may be overcome by adding to the material to be examined or cultured an agent or agents to impair the function of antibiotics previously administered to the patient. Paraminobenzoic acid impedes the action of the sulfonamides and penicillinase inactivates penicillin. A further procedure, often successful if the organisms cannot be demonstrated on smear or regular culture, is inoculation of growing chick embryo with the fluid. Growth is rapid in this medium—positive cultures may be obtained in six to eight hours—and antibiotic inhibition of growth is minimized, presumably because of the active circulation of the embryo.

It should be stressed that even if no bacteriological evidence can be elicited the diagnosis can be established on the basis of meningitis with associated hemorrhagic rash. When these petechiae or purpuric lesions are present, smear or culture of fluid drawn from them may reveal the organisms. Occasionally, the organisms are noted by an alert laboratory technician in the smear of the peripheral blood taken for the differential cell count.

At one time[29] the specific therapy of meningitis as a whole could be covered very simply: Once the diagnosis of purulent meningitis had been made, the patient was given polyvalent anti-meningococcus serum. If he had meningococcal meningitis, he had a chance of recovering; if not, he died. A more recent recommendation,[17] that all forms of meningitis be treated with penicillin given intraspinally, equally ignores the desirability of establishing the exact cause and using an appropriate specific agent in treatment. The modern diversity of specific agents has greatly improved the over-all prognosis.

Some observers[12, 27, 28, 30] are of the opinion that sulfonamide therapy alone is sufficient in most cases of meningococcal meningitis, and it is certainly the agent of prime importance. Others give a combination of penicillin and sulfonamide preference. Aureomycin[8] appears to be effective against the organism, but Long and co-workers[25] designated it as of undetermined value. The recommended dosages are given in Table 1. If the patient is unable to take oral medication, sulfadiazine may be given by hypodermoclysis as sodium sulfadiazine in a concentration of 0.5 to 1 per cent. (A 5 per cent solution may be used, but the risk of tissue slough makes it less desirable.) This subcutaneous route gives a desirable slow continued absorption and sustained blood level rather than the abrupt rise and fall obtained by intravenous administration. It is well, particularly initially, to check the blood levels of sulfadiazine and

TABLE 1.—*Therapy of Meningococcal Meningitis*
(Agents in order of preference)

Drug	Route	Initial Dose	Daily Dose	Level (Blood or serum)	Interval (Hours)	Duration
Sulfadiazine	Oral	75 mg./kg.	150 mg./kg.	12 to 15 mg.%	4	1 week after fever
	Parenteral (Subcut.)	75 mg./kg.	150 mg./kg.	12 to 15 mg.%	8	1 week after fever
Penicillin (Crystalline G)	Parenteral (Intramusc.)	500 to 1,500 u/kg. (0.3 to 1 mg./kg.)	4,000 to 15,000 u/kg. (2.7 to 10 mg./kg.)	>0.2 u/cc.	3	1 week after fever
Penicillin (Procaine G)	Parenteral (Intramusc.)	Not recommended	Same— After disease is under control	>0.2 u/cc.	12	1 week after fever
Aureomycin	Oral	10 to 20 mg./kg.	25 to 100 mg./kg.	.....	4 to 6	1 week after fever
	Parenteral (Intraven.)	5 mg./kg.	15 mg./kg.	.....	8	1 week after fever

adjust the dosage accordingly. The level should be 12 to 15 mg. per 100 cc.

Penicillin dosage calculated on a basis of body weight leads to undertreatment of infants and children because of disproportionate urinary excretion in this age group. It does serve as a rough guide, but the actual dosage should be overgenerously calculated. Although procaine penicillin is given once daily with excellent clinical results in the treatment of many bacterial infections, in the treatment of meningitis it is preferable to maintain optimal blood levels by administering the drug at 12-hour intervals. A range of dosage has been indicated for penicillin and aureomycin. If the infection is obviously more severe the larger dose should be given.

There is now far less enthusiasm for intraspinal injection of drugs than there was formerly, largely because of the effectiveness of administration by the oral and parenteral routes, and the undesirable irritative effects of intraspinal therapy. Hoyne[18, 19] has led the objectors and seems well sustained.[13] (Probably intraspinal therapy of meningitides should be limited to the treatment of tuberculous meningitis, as will be discussed later.)

Overwhelming infection represents great toxemia and requires the use of intravenous dextrose solution, plasma, blood, and supportive agents including large amounts of adrenal extract (whether or not there is evidence of adrenal failure dependent upon adrenal hemorrhage).

Influenzal meningitis now accounts for the majority of hospital admissions for meningitis in infancy and childhood.[10, 16] (Meningococcal meningitis formerly led in this respect, but the incidence has decreased as a result of early and vigorous treatment of febrile illness.) It is primarily a disease of this age group, but does occasionally occur in adults. Usually, the infant has had a respiratory infection—frequently of several weeks' standing. Listlessness, unexplained irritability, anorexia, vomiting and/or rise in temperature may lead the physician to consider central nervous system disease. The anterior fontanelle may be bulging, but if the infant has become severely dehydrated it may be sunken. The neck may or may not be stiff. Flexion of the neck is best tested by putting the infant in a sitting position and holding something attractive on his abdomen. Attempts to force flexion of a child's neck—be he sick or well—are usually met with stubborn resistance. Almost reflex flexion following extension of the neck over the edge of a table may be helpful in totally uncooperative infants and children.

It should be stressed that the diagnosis of meningitis in infancy may rest solely on the finding of purulent cerebrospinal fluid in an infant with unexplained fever.

Grossly and chemically the cerebrospinal fluid is similar to that found in meningococcal meningitis. Smears usually reveal a pleomorphic Gram-negative bacillus which is often incorrectly recognized morphologically because of prominent bipolar granules which give it the appearance of a diplococcus. The organism may be grown on suitable culture media. Inoculation of growing chick embryo may be of value for rapid identification. Organisms from smear or culture may be more definitely identified by the capsule swelling or "quellung" reaction produced by type B antiserum. This reaction is helpful in most instances. The leukocyte count is usually elevated with a polymorphonuclear response. Culture of exudate from foci of infection such as the throat or middle ear may reveal the organism.

Therapy (Table 2) prior to the advent of aureomycin consisted of sulfadiazine, streptomycin and antiserum. Alexander[1, 2, 3] outlined a plan of therapy in which the sugar content of the spinal fluid is used as the criterion of the severity of the disease. Most other observers, including the authors, employ antiserum in cases of unusual severity, using a single dose of from 50 to 200 mg. of immune nitrogen, the size of the dose depending on a rough estimate

TABLE 2.—*Therapy of Influenzal Meningitis*
(Agents in order of preference)

Drug	Route	Initial Dose	Daily Dose	Level (Blood or serum)	Interval (Hours)	Duration
Streptomycin (Dihydro-)	Parenteral (Intramusc.)	10 to 15 mg./kg.	40 to 60 mg./kg.	.....	4 to 6	5 days
Aureomycin	Oral	10 to 20 mg./kg.	25 to 100 mg./kg.	.....	4 to 6	2 weeks after fever
	Parenteral (Intraven.)	5 mg./kg.	15 mg./kg.	.....	8	2 weeks after fever
Sulfadiazine	Oral	75 mg./kg.	150 mg./kg.	12 to 15 mg.%	4	2 weeks after fever
	Parenteral (Subcut.)	75 mg./kg.	150 mg./kg.	12 to 15 mg.%	8	2 weeks after fever
Antiserum (Type B)	Parenteral (Intraven. or intramusc.)	50 to 200 mg.	Immune Nitrogen	.....	....	Administered once in most cases

Alexander recommends:		Spinal Fluid Sugar
	25 mg. immune nitrogen	Over 40 mg.%
	50 mg. immune nitrogen	25 to 40 mg.%
	75 mg. immune nitrogen	15 to 25 mg.%
	100 mg. immune nitrogen	Under 15 mg.%

Plus intrathecal streptomycin 25-50 mg. each day for 4-5 days.

of the severity of the disease and the size of the patient. The demonstrable presence of excess antibody in the serum may be used as a guide in extreme cases in which repeated administration is required. Antiserum should be diluted in several volumes of saline and given slowly so as to avoid the possibility of severe reactions. The use of either streptomycin or antiserum intraspinally is advised by some observers,[1, 2, 3, 36, 37] considered unnecessary and injurious by others.[15, 19]

Although reports are as yet incomplete, aureomycin appears to be superior in effectiveness to streptomycin and does not present the hazard of deafness caused by injury of the eighth nerve. Long and coworkers[25] suggested the combination of aureomycin and sulfadiazine as the therapy of choice. Chloramphenicol is apparently effective in vitro and probably is equally effective in vivo. Certainly, in the severe case, aureomycin, streptomycin, sulfadiazine and antiserum may be given in combination. Streptomycin can be discontinued by the fifth day with almost complete avoidance of injury to the eighth nerve.

Supportive measures, especially the judicious administration of fluids and blood, are of particular importance in this disease in which most of the patients are infants and young children. Recently, Ingraham and Smith[26, 31] emphasized the need for exploration and surgical drainage of fluid collections in the meninges following influenzal meningitis.

Even with optimal therapy the outlook for infants under nine months of age is poor. Bloor and coworkers[4] reported a mortality rate of over 40 per cent in this age group. In those who recovered there was a striking incidence of major and minor neurological disturbances. However, in private practice and with early diagnosis the results are better; the recovery rate is 90 per cent and there are few sequelae.

Pneumococcal meningitis may occur in any age group. It is frequently secondary to sinusitis—especially that involving the sphenoid sinus—and middle ear infections. The symptoms and signs are similar to those described for meningococcal meningitis except that the patient is liable to become comatose quickly. The results of blood examination are consistent with those of acute bacterial disease. The spinal fluid is almost cream-like in consistency in many instances. Smear and culture of the spinal fluid will usually reveal the organism which can then be typed as an aid in diagnosis as well as possible therapy with type-specific antiserum. The organism may also be recovered from the blood and from foci of infection.

Penicillin is the therapeutic agent of choice, but sulfadiazine should always be given concomitantly (Table 3). The value of aureomycin[25] and chloramphenicol is as yet incompletely determined. Type-specific antisera are used infrequently. The intraspinal route of administering therapeutic agents is used less than formerly, but would seem logical in cases in which there is actual empyema of the subarachnoid space. Dowling[14] stressed the use of massive intramuscular doses of penicillin — 1,000,000 units every two hours—without intraspinal or sulfonamide therapy. Neurological complications are frequent, but the percentage of patients with no sequelae is remarkably improved since the advent of penicillin therapy. In reviewing the cases of pneumococcal meningitis treated at Children's Hospital in San Francisco, it is of interest that there has been only one death since penicillin has been used in treatment, and the patient was moribund on admission. This is particularly remarkable in view of the small doses of penicillin that were given in the first months of its use. It should be emphasized, however, that no one agent should be relied upon and that therapy should be instituted as soon as a working diagnosis is established and fluid has been obtained for study. Surgical treatment of the primary focus of infection should be carried out concomitantly when indicated.

Colon bacilli are the cause of the most common form of meningitis in the neonatal period. Infection may be associated with an abrasion, or with anatomical defects such as spina bifida or meningocele; or the portal of infection may not be apparent. In this age period, signs and symptoms may be entirely lacking or may be similar to those observed in influenzal meningitis. Frequently, the disease is not diagnosed until autopsy following a sudden, unexplained neonatal death. Meningitis should be con-

TABLE 3.—*Therapy of Pneumococcal Meningitis*
(Agents in order of preference)

Drug	Route	Initial Dose	Daily Dose	Level (Blood or serum)	Interval (Hours)	Duration
Penicillin (Crystalline G)	Parenteral (Intramusc.)	1,500 to 15,000 u/kg. (1 to 10 mg./kg.)	15,000 to 170,000 u/kg. (10 to 110 mg./kg.)	1 to 2 u/cc.	2 to 3	1 week after fever, abnormal neurological signs
Penicillin (Procaine G)	Parenteral (Intramusc.)	Not recommended	Same—After disease under control	1 to 2 u/cc.	12	1 week after fever, abnormal neurological signs
(The upper dosage is that recommended by Dowling—1,000,000 units every 2 hours in adults)						
Sulfadiazine	Oral	75 mg./kg.	150 mg./kg.	12 to 15 mg.%	4	1 week after fever, abnormal neurological signs
	Parenteral (Subcut.)	75 mg./kg.	150 mg./kg.	12 to 15 mg.%	8	

sidered a possibility in an infant with unexplained fever and irritability. The spinal fluid is similar to that in influenzal meningitis. Organisms may be found on smear and culture of the spinal fluid and on culture of the blood.

Aureomycin[25, 32] and chloramphenicol appear to be the therapeutic agents of choice in infections by E. coli. Prior to the advent of these antibiotics,[12, 19] streptomycin and sulfadiazine were used with some success.

Obviously, diagnosis in neonatal infants is a greater problem than is therapy, but continued alertness plus the prophylactic use of antibiotics when predisposing conditions are present at birth should reduce the mortality from this source. The response to therapy in infancy is not good. Even though the responsible organism may be of low virulence, the host resistance is poor and antibiotic agents have a low degree of specificity.

The Salmonella organisms, including S. typhosa, cause meningitis on rare occasions. The disease is much like that caused by the colon bacilli. It usually occurs in young infants. Therapy includes the four antibiotics referred to in discussion of the treatment of E. coli meningitis. Chloramphenicol[25, 32] seems to be more effective than aureomycin in controlling most Salmonella infections. If possible the organism should be tested for sensitivity to the various agents, but because therapy must be started immediately, this cannot be done before treatment is under way. Because of the lack of specificity, more than one agent should be employed and the effectiveness of several explored by laboratory tests and clinical observation.

Streptococci and staphylococci may cause meningitis, but the incidence has dropped sharply with the rarity of mastoiditis now that specific therapy for otitis media is available. Before the use of antibiotics, infection of the middle ear often became chronic, led to mastoiditis, then to mastoidectomy with exploration of the lateral sinus, and finally to meningitis. The beta hemolytic streptococcus and staphylococcus aureus were the major offenders.

Therapy should be massive and combined—probably sulfadiazine, penicillin,[12, 25, 32] and aureomycin should be used in combination in large doses. As previous therapy may have rendered the organism resistant to one or more of the agents, sensitivity tests should be carried out. If resistance is observed, dosage may be increased or other agents tried.

Gonococcic meningitis is rare. Penicillin[25] is the therapeutic agent of choice, but all the available antibiotics have some effect. Sensitivity tests in vitro are invaluable in planning continued therapy in severe cases.

Tuberculous meningitis is an infrequent but ominous complication of tuberculous infection. It is thought to be associated with the primary spread of the infection, but the meningeal focus may remain quiescent for an indefinite period. In support of the association with primary tuberculous disease is the observation by European workers[9, 35] that the incidence of tuberculous meningitis has decreased out of proportion to the decrease in other forms of tuberculosis following the vaccination of large segments of the population with BCG.

The onset is usually insidious; rarely fulminant. The patient complains of malaise, has low grade fever, variable headache. Eventually this progresses to pronounced lassitude and coma. At this point neurological examination reveals evidence of meningeal irritation plus palsies and abnormal reflexes which change rapidly both in intensity and location. Convulsions are frequent. Diagnosis rests on these observations coupled with knowledge of previous tuberculous infection as evidenced by positive reaction to tuberculin skin test or by clinical tuberculosis. The tuberculin skin test reaction is usually positive, but it may be negative during the early primary invasion or in the presence of overwhelming disease (the tuberculin reaction having been formerly positive.)

Results of blood studies are not remarkable except for the accelerated sedimentation rate observed in tuberculous infection. There are fewer cells in the cerebrospinal fluid—usually 200 to 300—than in the usual bacterial meningitis. At the onset there may be a preponderance of polymorphonuclear leukocytes, but as a rule most of the cells are mononuclear. A smear of the sediment will reveal tubercle bacilli in some instances, but more often the organisms are found in the coagulated protein or pellicle on the top of the tube. Culture on suitable media and guinea pig inoculation will aid in demonstration of the organisms. The chemical abnormalities in the fluid are of particular interest. As in other bacterial infections involving the cerebrospinal fluid, there is lowering of the sugar content—often of pronounced degree. This diminution in sugar content is felt to be caused by the metabolic activity of the infecting organisms. Concomitant reduction in chloride content is usually noted and cannot be explained on the same basis. Perhaps the so-called "blood-brain barrier" is altered, resulting in spinal fluid chloride values that approximate the 100 mEq. per liter normal of blood rather than the 120 mEq. per liter normal of cerebrospinal fluid. Cerebrospinal fluid chloride content less than 105 mEq. per liter or 600 mg. per 100 cc. should be considered almost diagnostic of tuberculous meningitis.[20] The cerebrospinal fluid protein content is increased. Sometimes there is pleocytosis without other evidence of infection. The disease in such cases is referred to as "serous" meningitis, for which the prognosis is much better than it is for the usual form of tuberculous meningitis. The cause may be a form of "neighborhood" reaction in which tuberculous foci lie adjacent to the meninges.

To date, the most successful antibiotic for tuberculous meningitis is streptomycin.[6, 7, 11, 22, 23, 24, 33] This must be given intramuscularly and intraspinally. Dosage schedules are shown in Table 4. Even though with this dosage—4 gm. a day for the average adult — there is a great risk of deafness and

TABLE 4.—*Therapy of Tuberculous Meningitis*
(Agents in order of preference)

Drug	Route	Initial Dose	Daily Dose	Level (Blood or serum)	Interval (Hours)	Duration (Months)
Streptomycin (Dihydro-)	Parenteral (Intramusc.) (Intraspinal)	15 mg./kg.	60+ mg./kg. 50 to 100 mg.	....	4 to 6 24	2 to 6 1 to 3
Promizole	Oral	.....	1 to 8 gm. Gradual increase	1 to 3 mg.%	6	12 to 36
Paramino-Salicylic Acid	Oral	.....	10 to 15 gm.	.....	6	12 to 36

ataxia, the high mortality rate if smaller amounts of the drug are used makes this risk necessary. Dihydrostreptomycin has largely supplanted streptomycin, but damage to the eighth nerve still occurs in a significant percentage of cases. Promizole, paramino salicylic acid[5, 6, 7, 11, 22, 23, 24, 33] and other agents are sometimes used in conjunction with streptomycin with apparent benefit. Supportive measures are as important in management of tuberculous meningitis as they are in tuberculous infection generally and should not be overlooked in the pursuance of antibiotic regimens. Lincoln[22] stressed that the disease may progress even to coma during treatment, yet the patient recover. Lincoln,[6, 7, 11, 22, 23, 24, 33] DeBré and others report arrest of tuberculous meningitis in children in from 40 per cent to 70 per cent of cases. Results with adults are far less encouraging.

Fungi and molds cause meningitis rarely. Clinically, disease of the meninges caused by these agents is much like tuberculous meningitis. All available antibiotics have been used in treatment, with variable but inconspicuous success.

Aseptic Meningitides

A large number of disease entities of varying etiologic delineation are included among the aseptic meningitides. The common denominator is spinal fluid pleocytosis, with the number of cells varying from a few to a thousand or more. No bacteria or other large organisms are demonstrable. Clinically there is evidence of meningeal irritation, but encephalitis and/or myelitis may also be present. The cells in the cerebrospinal fluid are usually predominantly mononuclear, but in some instances, notably in the presence of acute anterior poliomyelitis, the polymorphonuclear leukocytes may exceed the mononuclear cells. The highest cell counts in aseptic meningitides are observed in mumps meningitis, in which there may be over a thousand cells, 90 to 95 per cent of them mononuclear. Other viral diseases of this group include western and eastern equine encephalitis, St. Louis encephalitis, Japanese B encephalitis, measles meningoencephalitis, chickenpox meningoencephalitis, lymphocytic choriomeningitis. There are other conditions in the aseptic meningitides category, such as infectious mononucleosis, which are probably of viral origin. Confirmation of the diagnosis by culture of the virus in chick embryos or laboratory animals or by demonstration of a rise in specific antibody titer during the course of the disease may be possible in some instances.

Therapy in this group is largely symptomatic, although aureomycin has been tried (inconclusively) in the treatment of mumps meningitis.

It is important to note that purulent meningitides which have been reduced in severity by partial treatment may be mistaken for aseptic meningitides. Since therapy is dictated by exact diagnosis, careful differentiation is essential. All the suggested diagnostic aids previously referred to must be kept in mind in trying to determine the infectious agent. Perhaps the chick embryo culture is the most valuable of all in coaxing the infecting cocci or bacilli to grow luxuriantly enough to be identified.

REFERENCES

1. Alexander, H. E., Ellis, C., and Leidy, G.: Treatment of type-specific Hemophilus influenzae infections in infancy and childhood, J. Ped., 20:673, June 1942.

2. Alexander, H. E., Leidy, G., Rake, G., and Danovich, B.: Hemophilus influenzae meningitis treated with streptomycin, J.A.M.A., 132:434, Oct. 26, 1946.

3. Alexander, H. E., and Leidy, G.: The present status of treatment of influenzal meningitis, Am. J. Med., 2:457, May 1947.

4. Bloor, B. M., and Grant, R. S.: Sequelae of meningitis due to Hemophilus influenzae, J.A.M.A., 142:241, Jan. 28, 1950.

5. Bogen, E., Loomis, R. W., and Will, D. W.: Para-aminosalicylic acid in treatment of tuberculosis, Am. Rev. of Tub., 61:226, Feb. 1950.

6. Brainerd, H. D., and Eagle, H. R.: The effects of streptomycin on tuberculous meningitis, Annals of Internal Medicine, Aug. 1950.

7. Bunn, P. A.: Specific therapy for tuberculous meningitis, Am. Rev. of Tub., 61:263, Feb. 1950.

8. Collins, M. S., Paine, T. F., Jr., and Finland, M.: Aureomycin in the treatment of pneumococcal pneumonia and meningococcemia, Proc. Soc. Exper. Biol. & Med., 69: 263, Nov. 1948.

9. Corach, L.: The treatment of tuberculous meningitis in the services of DeBré in Paris and of Cocci in Florence, La Prensa Med. Arg., 36:1620, Aug. 19, 1949.

10. Davison, W. C.: The Compleat Pediatrician, Duke University Press, 1949.

11. DeBré, R., Thieffry, S., Brissaud, H. E., and Noufflard, H.: Streptomycin and tuberculous meningitis in children. Preliminary note, Brit. Med. J., 2:897, Dec. 6, 1947. (See also 9.)

12. Dowling, H. F., Sweet, L. K., Hirsh, H. L., and Lepper, M. H.: Specific therapy of bacterial infections of central nervous system, J.A.M.A., 139:755, March 19, 1949.

13. Dowling, H. F., Sweet, L. K., Hirsh, H. L., and Lep-

per, M. H.: Specific therapy of bacterial infections of central nervous system, J.A.M.A., 139:755, March 19, 1949.

14. Dowling, H. F., Sweet, L. K., Robinson, J. A., Zellers, W. W., and Hirsh, H. L.: The treatment of pneumococcic meningitis with massive doses of systemic penicillin, Am. J. Med. Sci., 217:149, Feb. 1949.

15. Drake, M. E., Bradley, J. E., Imburg, J., McCrumb, F. R., and Woodward, T. E.: Aureomycin in the treatment of influenzal meningitis, J.A.M.A., 142:463, Feb. 18, 1950.

16. Foley, G. E., Shwachman, H., McGarry, M., and Winter, W. D., Jr.: Morphologic characteristic and antibiotic resistance of Hemophilus influenzae, Am. J. Dis. Child., 78: 659, Nov. 1949.

17. Hartman, A. F., Love, F. M., Wolff, D., and Kendall, B. S.: Diagnosis and management of severe infection in infants and children: A review of experiences since the introduction of sulfonamide therapy, J. Ped., 27:115, Aug. 1945.

18. Hoyne, A. L.: Improved methods in treatment of meningitis, Miss. Val. Med. J., 66:9, Jan. 1944.

19. Hoyne, A. L., and Brown, R. H.: Intrathecal therapy not required for H. influenzae meningitis, J.A.M.A., 136: 597, Feb. 28, 1948.

20. Joffe, H. H., and Well, A. N.: Laboratory studies of cerebrospinal fluid in meningitis and poliomyelitis, Minnesota Med., 32:608, June 1949.

21. Kempe, C. H., Shaw, E. B., and Silver, H. K.: Clinical applications of chick embryo cultures: I. Primary diagnosis of meningitis and study of spinal fluid in meningococcemia without meningitis. II. In vivo streptomycin sensitivity test, A. M. J. Dis. Child., 72:281-288, Sept. 1946.

22. Lincoln, E. M., Kirmse, T. W., and DeVito, E.: Tuberculous meningitis in children, J.A.M.A., 136:593, Feb. 28, 1948.

23. Lincoln, E. M., and Kirmse, T. W.: Streptomycin and promizole in miliary tuberculosis and tuberculous meningitis, Lancet, 1:767, May 7, 1949.

24. Lincoln, E. M., and Kirmse, T. W.: Streptomycin-promizole therapy of miliary and meningeal tuberculosis in children, Am. Rev. of Tub., 61:159, Feb. 1950.

25. Long, P. H., Chandler, C. A., Bliss, E. A., Bryer, M. S., and Schoenbach, E. B.: The use of antibiotics, J.A.M.A., 141:315, Oct. 1, 1949.

26. McKay, R. J., Morrissette, R. A., Ingraham, F. D., and Matson, D. D.: Collections of subdural fluid complicating meningitis due to Haemophilus influenzae (Type B), N.E.J.M., 242:20, Jan. 5, 1950.

27. Meads, M., Harris, W., Sampler, B., and Finland, M.: Treatment of meningococcus meningitis with penicillin, N.E.J.M., 231:509, Oct. 12, 1944.

28. Page, S. G., and Page, M. J.: Sulfadiazine in the treatment of meningococcic meningitis, Virg. Med. Month., 75:397, Aug. 1948.

29. Shaw, E. B., and Thelander, H. E.: Meningococcus infection—its treatment, Calif. and West. Med., 31:1, Nov. 1929.

30. Shaw, E. B.: Meningococcus disease, Calif. and West. Med., 61:240, Nov. 1944.

31. Smith, M. H. D., et al.: Subdural effusions complicating acute bacterial meningitis. To be published. (See 26.)

32. Spink, W. W., and Yow, E. M.: Aureomycin: Present status in the treatment of human infections, J.A.M.A., 141: 964, Dec. 3, 1949.

33. Su, T. F., and Wu, M. Y.: Streptomycin and promizole combined therapy in tuberculous meningitis in children, J. Ped., 36:295, March 1950.

34. Veras, S., and Mystakidis, A.: Escheria coli meningitis treated successfully with streptomycin, Am. J. Dis. Child., 79:115, Jan. 1950.

35. Wallgren, A.: Personal communication.

36. Weinstein, L.: The treatment of meningitis due to Hemophilus influenzae with streptomycin, N.E.J.M., 235: 101, July 25, 1946.

37. Yampolsky, J., and Jones, J. P.: Present treatment of influenzal meningitis, Am. J. Dis. Child., 78:97, July 1949.